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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/578,840	02/16/2007	Yasufumi Kikuchi	060641-0113	2215

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EXAMINER	
HADDAD, MAHER M	
ART UNIT	PAPER NUMBER
1644	
MAIL DATE	DELIVERY MODE
02/11/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/578,840	KIKUCHI ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 October 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24,27,29,31,33 and 38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24, 27, 29, 31, 33 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05/10/2006 and 11/12/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/25/2010 has been entered.

2. Claims 24, 27, 29, 31, 33 and 38 are pending and under consideration in the instant application are under examination as they read on a humanized antibody binding to CD47 and a therapeutic agent thereof and the humanized MABL-2 antibody HL5, SEQ ID NO: 73 (now SEQ ID NO: 110/113) and SEQ ID NO: 99 and 106.

3. Applicant's IDS, filed 05/10/2006 and 11/12/2009, is acknowledged.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 24, 27, 29, 31, 33 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP001167388A1 in view of Sato et al., (Cancer Res., 53, 851-856 (1993)) as is evidenced by the specification under Example 1.

The `388 publication teaches and claims a single-chain Fv which is a humanized single-chain Fv capable of inducing apoptosis of cells having Integrin Associated Protein (IAP) (see published claim 10). An H and L chain V region of MABL-2 which is a humanized L chain V region (see published claims 4-5 and 10-11 and SEQ ID NOs:7-8). A humanized monoclonal antibody or a fragment thereof which can be prepared from a humanized single-chain Fv capable of inducing apoptosis of cells having Integrin Associated Protein (IAP) (see published claim 13). The `388

publication teaches that the results show that the single-chain Fv of MABL-2 antibody (MABL2-scFv) remarkably induced human IAP specific cell death of L1210 cells (Figures 13-16) and that the single-chain Fv also induced cell death of CCRF-CEM cells in comparison with the control (see ¶154 and Figures 17-18). The `388 publication teaches in order to clone a DNA encoding the V region of the mouse monoclonal antibodies for human IAP, mRNAs are prepared from cells producing the mouse monoclonal antibody and converted to double strand cDNAs by a known method and the desired DNA is amplified from the cDNAs by polymerase chain reaction (PCR) method. As a source of mRNAs, a hybridoma producing a monoclonal antibody to human IAP should be prepared. Such hybridomas MABL-2 (FERM BP-6101) (see ¶29). The oligonucleotide primers of SEQ ID No.: 1 and SEQ ID No.: 2 are used as 5'-end and 3'-end primers, respectively, in order to amplify the L chain V region of the MABL-2 antibody (¶31). Table 1 show the heavy and light chain CDRs of the MABL-2. The `388 publication teaches the reconstructed single-chain Fv according to the present invention can be humanized by using conventional techniques. Once a DNA encoding a humanized Fv is prepared, a humanized single-chain Fv, a fragment of the humanized single-chain Fv, a humanized monoclonal antibody and a fragment of the humanized monoclonal antibody can readily be produced according to conventional methods. Preferably, amino acid sequences of the V regions thereof are partially modified, if necessary (see ¶19, ¶23, ¶56). The `388 publication teaches that MABL-2 antibody is IgG2a, κ type (see ¶88) and has the MABL-2 antibody has a κ type L chain and a γ2a type H chain (see ¶30).

The reference teachings differ from the claimed invention only in the recitation of specific human heavy and light framework in claims.

Sato et al teach that mouse antibodies, however, are highly immunogenic in human patients. For this reason, their therapeutic value in human patients is limited. In order to be effective as therapeutic agents administered to human patients in repeated doses, mouse antibodies must be engineered to look like human antibodies. The most complete humanization of a mouse antibody is achieved by grafting the CDRs from the mouse antibody into a human antibody to recreate a good, functional antigen-binding site in a reshaped human antibody (see page 851, 1st col., 2nd ¶). Sato et al teach the creation of a reshaped human antibody that is equivalent to the original mouse antibody in terms of binding and inhibition (see page 851, 2nd col., 1st ¶). Sato et al teach that the mouse PM-1 light and heavy chain variable regions belong to mouse kappa light chain subgroup I and mouse heavy chain subgroup II, respectively. With respect to human antibodies, the mouse PM-1 light and heavy chain variable regions were most similar to REI (72.2%), a member of human κ light chain subgroup I, and VAP (71.8%), a member of human heavy chain subgroup II, respectively (see page 852, under Results). Sato et al teach that as shown in Fig. 3, two version fo reshaped human PM-1 light chain variable region were designed. In version a, the human FRs were identical to the REI-based FRs present in the reshaped human CAMPATH-1H. REI is a member of subgroup I of human kappa light chain variable regions. Mouse PM-1 kappa light chain variable region is most similar to this human subgroup. Version b was based on version a with only one amino acid change at position 71 in human FR3. Residue 71 is part of the canonical structure for L1 and may, therefore, influence antigen binding. For the reshaped human PM-1 heavy chain variable region, six versions were designed. In all six

versions, the human FRs were based on the NEW FRs present in reshaped human CAMPATH-1H. NEW is a member of subgroup II of human heavy chain variable regions and shows 68.4% similarity to mouse PM-1 heavy chain variable region . Seven amino acid residues in the human FRs (positions 1, 27, 28, 29, 30, 48, and 71) were identified as having a possible adverse influence on antigen binding. In the model of mouse PM-1 variable regions, residue 1 is a surface residue that is located close to the CDRs. Residues 27 to 30 are part of the canonical structure for Hl (31) and are observed in the PM-1 model to form part of the H l loop. These residues, therefore, are likely to be directly involved in antigen binding. Residue 48 is buried under the H2 loop and, therefore, may be influencing the conformation of this loop. Residue 71 is part of the canonical structure for H2 (31-33). In the model, it appeared that Arg-71 influences both the H1 and H2 loop conformations by forming hydrogen bonds with Thr-30, Asp-32, and Ser-54. See page 852, under Design of Reshaped Human PM-1 variable Regions)

Sato et al. do not teach humanizing the MABL-2 specific antibodies of the instant invention, however, one of ordinary skill in the art at the time the invention was made would have been motivated to do so for any antibody intended for various therapeutic use in humans. The resultant humanized MABL-2 antibody would comprise the claimed FRs. The resultant humanized antibodies would comprises the claimed sequences as is evidenced by the specification under Example 1 that FR1-FR4 of the MABL-2 were identical with FR1-Fr4 of the human antibody AF216824/HSJC11VJ and the CDRs were identical with the CDRs in the H chain V region of the mouse MABL-2 antibody (see page 43, lines 1-4 and page 48, lines 25-28).

Therefore, from the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention was a whole is prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

6. The 7,696,325 and 7,531,643 are listed on the PTO-892 because they claim the mouse MABL-1 antibody.

7. No claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

February 8, 2011

/Maher M. Haddad/
Primary Examiner,
Art Unit 1644